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Gene Section
Review

PCNA (proliferating cell nuclear antigen)

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Identity

Other names: MGC8367

HGNC (Hugo): PCNA

Location: 20p12.3

DNA/RNA

Description

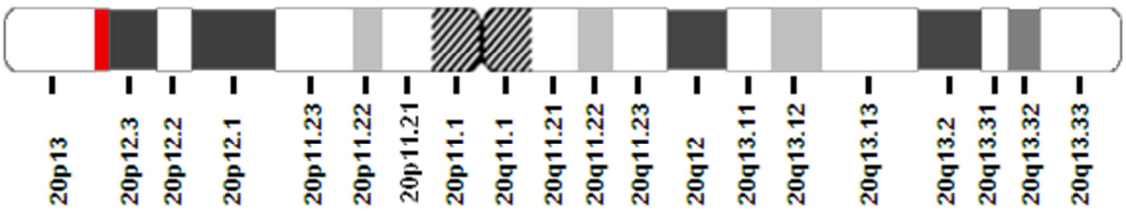
The PCNA gene is situated on human chromosome 20 and it spans about 12 kb. It is a single-copy gene, however, several pseudogenes have been noted. The precise localization of the PCNA gene is at the border of two histological G-bands (p12.3 and p13) (Webb et al., 1990), thus it is reported in both locations depending on the probe used. The human PCNA gene was first cloned and characterized in 1989 by Travali and co-workers (Travali et al., 1989).

Transcription

There are two reported gene transcripts, which encode the same protein.

PCNA transcript variant 1 is 1355 bp long after the completion of mRNA splicing. It has NCBI Reference Sequence code NM_002592.2 (NCBI). The PCNA transcript variant 1 has seven exons, six of which are contributing to the protein sequence. The first intron is relatively large in comparison with the other PCNA transcript variant. Following the splicing the length of the transcript is shortened to about 12% of that of the initial transcript. The translation starts from the middle of the 2nd exon and ends in the beginning of 7th exon. The product is a full length protein, designated as NP_002583.1 (NCBI), with 261 amino acids.

PCNA transcript variant 2 is 1319 bp long after the completion of mRNA splicing.



The localisation of the PCNA gene (in red) at the interface between 20p12.3 and 20p13 histological bands on chromosome 20.

	NCBI Reference Sequence	Length (unspliced)	Length (spliced)	Exons	Protein	AA
PCNA transcript variant 1	NM_002592.2	11670 bp	1355 bp	7	NP_002583.1	261
PCNA transcript variant 2	NM_182649.1	5049 bp	1319 bp	6	NP_872590.1	261

It has NCBI Reference Sequence code NM_182649.1 (NCBI). The PCNA transcript variant 2 has six exons, which are contributing to the protein sequence. After the splicing the length of the transcript is shortened to about 26% of that of the initial transcript. Translation starts from the end of the 1st exon and ends in the beginning of 7th exon. The product is a full length protein, designated as NP_872590.1 (NCBI), with 261 amino acids.

Pseudogene

PCNAP - one pseudogene on human chromosome X - p11 (Ku et al., 1989; Webb et al., 1990).
PCNAP1 and PCNAP2 - two pseudogenes in tandem on human chromosome 4 - q24 (Taniguchi et al., 1996).
There are several other possible pseudogenes:
LOC390102 on chromosome 11 - p15.1 (Webb et al., 1990), LOC392454 on chromosome X - p11.3 (Ku et al., 1989; Webb et al., 1990).

Protein

Description

The human PCNA protein is a polypeptide of 261 amino acids and theoretical molecular weight of about 29 kDa. The functional protein is a homotrimer, build from three identical units interacting head-to-tail and forming a doughnut shaped molecule. There is an evidence for the existence of a double homotrimer in vivo (Naryzhny et al., 2005).

Expression

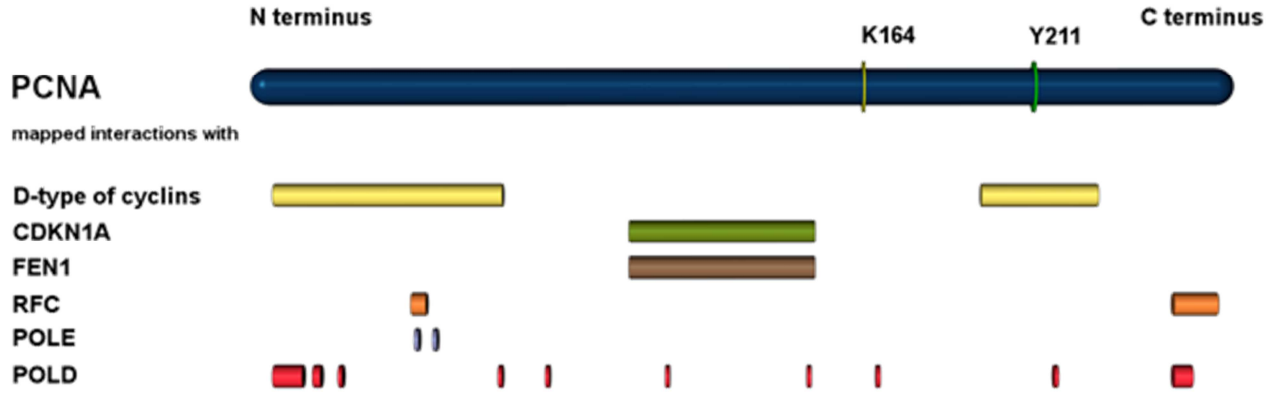
Expressed in nearly all proliferating tissues with high levels detected in thymus, bone marrow, foetal liver and certain cells of the small intestine and colon.

Localisation

PCNA is exclusively localized in the nucleus. It can be detected by immunofluorescence in all proliferating nuclei as discrete nuclear foci, representing sites of ongoing DNA replication and/or DNA repair.

Function

PCNA was originally discovered as an antigen, reacting with antibodies derived from sera of patients with systemic lupus erythematosus (Miyachi et al., 1978). The first assigned function of the PCNA protein is as an auxiliary factor of polymerase delta (Tan et al., 1986; Prelich et al., 1987). Later it was suggested that PCNA functions as a cofactor to many other eukaryotic polymerases such as polymerase epsilon, polymerase beta and several specialised polymerases known as translesion synthesis polymerases (eta, kappa, lambda, theta, etc.), with which PCNA is known to interact (Naryzhny, 2008). The role of PCNA in DNA replication is thoroughly investigated and PCNA is proposed to serve as a switch between the priming polymerase alpha and replicative polymerases (delta and epsilon) and functioning as a cofator of the latter polymerases. Complementary to enhancing the processivity of DNA replication, PCNA is known to coordinate the maturation of Okazaki fragments through interaction with FEN1 and stimulation of the flap endonuclease activity. PCNA interacts with large number of proteins, suggesting many functions in vivo (Naryzhny, 2008; Stoimenov and Helleday, 2009). There is evidence, derived from experiments in yeast, that PCNA may be involved in the establishment of sister chromatid cohesion in S phase of the cell cycle (Moldovan et al., 2006). PCNA is an indispensable factor for different DNA repair pathways including mismatch repair, nucleotide excision repair and sub-pathways of base excision repair. There is a growing body of evidence for the function of PCNA in the chromatin remodelling and organisation. The interaction of PCNA and CAF1 is in the heart of the nucleosome assembly, while the chromatin modification is also known to be regulated by PCNA through the known interaction with DNMT1 and HDAC1.



PCNA and mapped interactions with several proteins (D-type of cyclins, CDKN1A, FEN1, RFC complex, polymerase epsilon and polymerase delta). Two residues are highlighted, lysine at position 164 (site of ubiquitylation) and tyrosine at position 211 (site of phosphorylation).

One of the most stable interactions of PCNA is that with the cyclin-kinase inhibitor CDKN1A, which suggests a role of PCNA in the cell cycle progression. Another evidence for the involvement of PCNA in the cell cylcle control is the interaction with cyclin-D. Several amino-acid residues are post-translationally modified, suggesting even more complex functions (Stoimenov and Helleday, 2009). PCNA could be subjected to post-translational phosphorylation, acetylation, methylation, ubiquitylation and SUMOylation.

Implicated in

Note

The absence of the proliferating nuclear cell antigen (PCNA) protein is embryonic lethal in mice (Roa et al., 2008; Peled et al., 2008). The embryonic lethality in mice also suggests a critical importance of the PCNA protein for humans at least in proliferating tissues (Moldovan et al., 2007). The knockout mice for PCNA ($Pcna^{-/-}$) are dying in embryonic state, consistent with the role of PCNA in orchestrating DNA replication (Moldovan et al., 2007). In addition to this fact, there are no known mutations of the PCNA protein in humans, which therefore leads to a speculation that PCNA is so vital that any alternation of its sequence would have deleterious consequences. One suggestion for such essential function is the fact that both sequences of the PCNA protein and of the respective gene are highly conserved during evolution (Stoimenov and Helleday, 2009). Indeed, a human population study of PCNA polymorphisms shows only 7 intronic single nucleotide polymorphisms (SNP) and 2 synonymous exonic SNPs (Ma et al., 2000).

According to OMIM and Human Locus Specific Mutation Databases there is no known disease, which is caused by mutation or loss of function of the PCNA protein.

The only implication of PCNA in human disease is as a prognostic or diagnostic marker, sometimes used together with other markers. The utilisation of PCNA as a marker is very much restricted to an illustration of proliferation potential and therefore cannot be specific for any disease. However, PCNA is indeed used as a prognostic and diagnostic marker in several human diseases in clinical practice, as shown below. The list is far from complete since any human disease associated with proliferation could utilise PCNA as a marker.

Primary breast cancer

Note

A group of patients with high PCNA labeling index was associated with poor overall survival compared with the low PCNA labeling index group in several immunohistochemical studies (Horiguchi et al., 1998; Chu et al., 1998). PCNA labeling index is stated to be an independent predictor in primary breast cancer patients (Horiguchi et al., 1998) with a prognostic value (Chu et al., 1998).

Chronic lymphoid leukemia (CLL)

Note

There are attempts to correlate the levels of the PCNA protein in cells derived from patients with chronic lymphoid leukemia and the prognosis of survival (del Giglio et al., 1992; Faderl et al., 2002). The high level of PCNA in the cells of CLL patients suggests a higher proliferative activity and potentially shorter survival (del Giglio et al., 1992). Intracellular levels of PCNA protein can be used as marker to predict clinical behaviour and overall survival in patients with CLL (Faderl et al., 2002).

Non-Hodgkin's lymphoma

Note

In studies conducting immunohistochemical staining of materials from patients with non-Hodgkin's lymphoma, PCNA labeling index together with AgNOR score can be used to predict overall survival (Korkolopoulou et al., 1998). PCNA is the only independent predictor of the post-relapse survival and the histologic grade, which is the most important indicator of disease-free survival (Korkolopoulou et al., 1998).

Malignant and nonmalignant skin diseases

Note

In one study of comparison between malignant skin diseases (squamous cell carcinoma, adult T lymphotrophic leukemia, mycosis fungoides, malignant melanoma and malignant lymphoma) and nonmalignant skin diseases (resistant atopic dermatitis, psoriasis vulgaris, verruca vulgaris) the anti-PCNA staining was used as a prognostic marker (Kawahira, 1999). The percentage of PCNA-positive cells reported in the study was higher for malignant skin diseases in comparison with the non-malignant skin deseases (Kawahira, 1999). The localization of PCNA-positive cells was found to be in the dermis and the basal layer in case of the malignant skin diseases, whereas in the nonmalignant skin diseases PCNA-positive cells were detected only in the basal layer (Kawahira, 1999). The PCNA labeling index and the distribution of PCNA-positive cells in the skin were suggested to be helpful in the early diagnosis of skin malignancies.

Systemic lupus erythematosus (SLE)

Note

The anti-PCNA antibodies were originally found in patients with systemic lupus erythematosus (Miyachi et al., 1978), most of whom had diffuse proliferative glomerulonephritis in a small clinical study (Fritzler et al., 1983).

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